Respiratory Medicine (2006) **100**, 2207–2219

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Detection of changes in respiratory mechanics due to increasing degrees of airway obstruction in asthma by the forced oscillation technique☆

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Received 5 October 2005; accepted 9 March 2006

KEYWORDS
Asthma;
Forced oscillation technique;
Spirometry;
Respiratory mechanics

Summary Forced expiratory airflows and volumes are often used to assess the airway obstruction in asthmatics. However, forced maneuvers may change bronchial tone and modify airway patency. The aim of this study was to determine whether the Forced Oscillation Technique (FOT), which does not require forced manoeuvres, may be useful to describe the changes in respiratory mechanics in progressive asthma. This study involved 25 healthy and 84 asthmatics, including patients with normal spirometric exam (NE), mild moderate and severe obstruction. Resistive data were interpreted using the respiratory system resistance extrapolated at 0 Hz (R0), the mean respiratory resistance (Rm), and the resistance/frequency slope (S). Reactance data were interpreted by its mean values (Xm), the dynamic compliance (Crs,dyn), and resonant frequency (fr). Receiver operating characteristics curves were used to determine the sensitivity (Se) and specificity (Sp) of FOT parameters in identifying asthma.

There were not statistically significant differences between the control and NE groups. Comparing the control and mild groups, significant increases of R0 ($P<0.0007$), Rm ($P<0.003$), and S ($P<0.003$) were observed. In reactive parameters, a significant reduction in Crs,dyn ($P<0.04$) was observed, while Xm and fr presented significant increases ($P<0.0007$ and $P<0.006$, respectively). Comparison between mild and moderate groups showed non-significant modifications in all of the parameters, except for Xm ($P<0.02$). In the late stages (moderate

☆Supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico—CNPq and Fundação de Amparo a Pesquisa do Estado do Rio de Janeiro—FAPERJ.

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doi:10.1016/j.rmed.2006.03.009

to severe obstruction), all of the resistive parameters, as well as the reactive ones Xm ($P<0.007$) and Crs,dyn ($P<0.03$), presented statistically significant modifications. Among the studied parameters, the effects of airway obstruction in asthma seem to be well described by R0, Rm, S and Xm, which were in close agreement with physiological fundamentals. The best parameters for detecting asthma were R0 (Se = 81%, Sp = 76%), S (Se = 78%, Sp = 72%) and Xm (Se = 81%, Sp = 80%).

In conclusion, the results of this study suggest that the FOT can be proposed as an alternative method for the assessment of the respiratory mechanics in asthmatic patients, representing a promising solution to the problem of effort dependence.

Introduction

The treatment of asthma is based on its severity, which is determined by symptoms and evaluations of respiratory mechanical alterations. The disturbances associated with the asthma pathophysiology promote an increase of the airways obstruction that affects the whole tracheobronchial tree, mainly the small calibre airways.[1] The elastic properties of the respiratory system are also modified in these patients due to lung hyperinsuflation and modifications in the airway walls. Usually, airway obstruction and elastic properties are indirectly evaluated by measuring the resultant expired airflows and volumes using spirometry. These tests, however, requires a high degree of collaboration and maximal effort on the part of the subject. Accordingly, these measurements may be unreliable and variable if suboptimal manoeuvres are performed.[2] Furthermore, forced inspiratory and expiratory manoeuvres may change bronchial tone and modify airway patency, rendering the indices obtained hardly physiologic.[2] Whole body plethysmography is another useful technique to measure airway obstruction in asthmatics, although it also needs a high degree of collaboration and maximal effort.

A promising solution to the problem of effort dependence may be the measurement of lung function using the Forced Oscillation Technique (FOT), since it requires minimum cooperation by the subject. Another important advantage is the detailed characterization of the resistive and reactive properties of the respiratory system over a wide range of frequencies provided by this technique,[3–6] offering a complementary point of view, and contributing to increase our understanding concerning the pathophysiologic mechanisms involved in asthma.[2] FOT has been successfully applied to obtain a detailed analysis of several aspects of the abnormal respiratory mechanics in asthmatic subjects, including the evaluation of adults[7,8] and pediatric patients,[9,10] as well as bronchodilator response[11] and the effect of postural changes.[12] However, there are few data in the literature concerning the influence of the progression of airflow obstruction evaluated by spirometric measurements in the total respiratory resistance and reactance in adult asthmatic patients.[13]

Objective

In this context, the aim of the present study was to investigate the ability of FOT to detect the effects of increasing degrees of airway obstruction in asthmatic patients. First, the abnormal effects of the increasing in airflow obstruction, as determined by the reduction in spirometric volumes and flows, on respiratory resistance and reactance curves are presented and discussed. Then, their influences on FOT resistive and reactive parameters are investigated and, finally, the sensitivity and specificity of the FOT parameters in identifying asthma were analysed.

Patients and methods

This study was approved by the local Ethics Committee and is in agreement with the declaration of Helsinki. Informed consent was obtained from all volunteers before inclusion in the study.

Patient selection

This study involved 109 volunteers, divided as follows: Twenty-five were healthy individuals who had no history of pulmonary or cardiac disease, or even tobacco use (control group). Eight-four were patients with clinical diagnosis of asthma referred to the clinical pulmonary function laboratory. The diagnostic of asthma was based on the presence of dyspnoea, chronicle coughs, squeeze in the chest or thoracic uncomfort. The spontaneous improvement of these symptoms after the bronchodilator use was also an indicative of asthma ($>12\%$ improvement of forced expiratory volume for the 1 s (FEV_1) predicted baseline after β_2-agonist inhalation). Exclusion criteria for this study were the inability to perform technically adequate spirometry or FOT measurements, smoking history, evidence of current airway infection, acute exacerbation or any cardio-respiratory disease other than asthma. The exams were carried out in a random sequence and the delay between them was less than thirty minutes. All patients were in stable clinical condition. Baseline data, including age, sex, height and weight were obtained from each patient at time of procedures.

Spirometry and classification of the degree of airway obstruction

Using a closed circuit spirometer (*Vitrace VT-139; Pro-médico, Rio de Janeiro, Brazil*), measurements for forced vital capacity (FVC), FEV_1, FEV_1/FVC, and the ratio of forced expiratory flow (FEF) between 25% and 75% of FVC to FVC (FEF/FVC), were obtained for patients in a sitting position. These parameters were presented as raw data and percentile of the predicted values (% pred). Predicted values for spirometry were obtained from Knudson et al.,[14] and Pereira et al.[15] Forced expiratory manoeuvres were repeated until three sequential measurements were obtained. The indexes studied were those obtained through the better curve, which was selected based on the higher value of FEV_1 plus FVC. Quality control of spirometry is given by the ATS criteria, with the software allowing detection of non-acceptable manoeuvres.

Asthmatic individuals were divided in four classes based in the degree of airway obstruction. The airway obstruction classification used in the present work[16,17] was based on FEF_{25-75}/FVC and FEV_1/FVC relationships. These parameters are considered a precocious indicator of airway obstruction,[18] and associated with the diffuse airway obstruction,[19,20] respectively. This way, FEF_{25-75}/FVC was used in the classification of the obstruction in its initial phases and FEV_1/FVC in the classification in the most advanced phases. The boundaries chosen to subdivide the patients are dependent on the individual's age, as described in Table 1.

Twenty-one patients, with clinical diagnosis of asthma and normal respiratory response by spirometry, constitute the group called "normal to the exam—NE". Other 63 asthmatic patients, including mild ($n = 25$), moderate ($n = 23$) and severe ($n = 15$) airflow obstruction, were also studied.

Forced oscillation technique

The FOT instrument used in this study has been described in detail previously.[21,22] In short, the patient was seated with the head in a normal position and breathing quietly via a screen pneumotachograph. A small amplitude (smaller than 2.0 cmH_2O) pseudorandom noise pressure signal containing all harmonics of 2 Hz from 4 to 32 Hz was applied at the mouth by means of a loudspeaker. The volunteer was asked to hold their cheeks and the mouth floor with their hands in order to minimize the upper airways shunt. The measurements were conducted during tidal breathing at FRC. Mouth pressure and flow were recorded using identical differential pressure transducers (Honeywell, 176PC) and then, after analogue-to-digital conversion, fed to a Fourier analyser which performs an ensemble averaging over a time of 16 s and calculates the impedance of the respiratory system in each frequency applied. The impedance is partitioned in a real part or resistance (Rrs), in which flow is in phase with the pressure signal, and imaginary part, or reactance (Xrs), which express the ratio of the 90° out of phase component of pressure to mouth flow. The final result of the test was calculated by the mean of three 16 s measurements, each one started 30 s after the beginning of the exam in order to allow the volunteer to accommodate to the equipment. A coherence function is also obtained at each frequency investigated in order to evaluate the accuracy of the measurements. Only exams with a minimal coherence function of 0.9 were considered adequate.[23,24] When the coherence computed for any

Table 1 Boundaries used to subdivide patients into mild, moderate and severe subgroups.

	36–45 years			46–55 years			≥56 years		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
FEF/FVC (%)	58	—	—	46	—	—	46	—	—
FEV_1/FVC (%)	—	64	49	—	63	48	—	62	47

of the studied frequencies was less than this threshold, the manoeuvre was not considered valid and was repeated. Whenever correct manoeuvres could not be obtained according to these criteria, the patient was excluded from the study.

Data processing, presentation and statistical analysis

To describe the resistive component of the FOT data, an analysis of linear regression in the frequency range between 4 and 16 Hz was used in order to achieve intercept resistance (R0) and the slope of the resistive component of the impedance (S). These parameters are associated with the total resistance of the respiratory system[24] and with the respiratory system non-homogeneity,[25,26] respectively. Using the same frequency range, a parameter commonly related to airways resistance, the mean resistance (Rm) was also calculated.[4]

The results associated with the reactance were interpreted using three parameters: the mean reactance (Xm), the resonance frequency (fr) and the dynamic compliance of the respiratory system (Crs,dyn). The mean reactance is usually related to respiratory system non-homogeneity,[27] and, in this study, was calculated using the frequency range from 4 to 32 Hz. The frequency in which Xrs becomes zero is denominated resonance frequency. There is no energy accumulation in this frequency because respiratory compliance and inertance are equal and opposite in magnitude, and only dissipative elements are present. When respiratory mechanical alterations resulted in an fr value higher than 32 Hz, an extrapolation based on a third order polynomial was used in order to achieve this parameter. The equation $Crs,dyn = -1/(2\pi f Xrs)$ was used to estimate Crs,dyn. This parameter was calculated using Xrs at 4 Hz and reflected the airways, lungs and chest wall compliances.[4]

The statistical procedures were performed with a commercial software package (STATISTICA for Windows, release 5.0). The results are presented as mean $\pm$ standard deviation, with a box plot graphical description. One-way ANOVA, further corrected by Bonferroni's method, was used when the achieved data presented a statistically normal distribution. On the other hand, a non-parametric test (Kruskal–Walis), associated with a Mann–Whitney *U*-test was applied when there was no normal distribution. A *P*-value of less than 0.05 was considered statistically significant. In order to assess the sensitivity and specificity of FOT indices for the diagnosis of airway obstruction in asthma, receiver operating characteristic (ROC) curves were constructed. These curves were elaborated using SPSS release 10.0. The first part of this analysis was performed excluding the asthmatics with normal response by spirometry. In the second part, these asthmatics were included in the control group, since they were considered normal by spirometry.

Results

The age distribution, physical characteristics and spirometric parameters of the studied subjects are summarized in Table 2. As can be seen in the statistical analysis, the five groups were of similar

Table 2 Biometric and spirometric characteristics of the studied subjects.

	Group A Control ($n = 25$)	Group B Normal to the exam ($n = 21$)	Group C Mild ($n = 25$)	Group D Moderate ($n = 23$)	Group E Severe ($n = 15$)	
Age (years)	42.5 ± 16.2	38.4 ± 17.3	42.8 ± 16.2	48.5 ± 17.6	54.0 ± 19.8	ns/A,B,C,D,E
Weight (kg)	63.0 ± 11.5	67.5 ± 18.9	66.4 ± 14.7	64.3 ± 12.0	67.8 ± 13.3	ns/A,B,C,D,E
Height (cm)	160.0 ± 10.0	159.7 ± 9.7	159.6 ± 10.9	159.2 ± 11.6	161.2 ± 8.0	ns/A,B,C,D,E
Male/Female	7/18	4/17	5/20	9/14	8/7	–
FEV_1 (L)	3.0 ± 1.2	2.9 ± 0.9	2.2 ± 0.7	1.6 ± 0.8	1.0 ± 0.4	0.001/A,B,C,D,E
FEV_1 (%pred)	101.4 ± 20.1	102.8 ± 14.1	79.4 ± 12.8	54.2 ± 16.9	39.2 ± 11.1	0.001/A,B-C-D-E
FVC (L)	3.4 ± 1.2	3.5 ± 1.0	3.2 ± 1.0	2.7 ± 1.2	2.4 ± 0.8	0.001/A,B,C,D,E
FVC (%pred)	99.0 ± 18.2	105.3 ± 14.7	94.8 ± 16.6	79.4 ± 22.2	75.5 ± 19.6	0.001/A,B,C-D,E
FEF/FVC (%)	106.8 ± 24.8	88.7 ± 21.1	51.6 ± 13.5	26.9 ± 5.8	15.7 ± 4.4	0.001/A,B-C-D-E
FEV_1/FVC (%)	85.3 ± 6.2	83.0 ± 5.6	70.4 ± 3.8	57.1 ± 5.0	42.3 ± 4.6	0.001/A,B-C-D-E

n: number of subjects; Comparisons of the five groups/comparisons between adjacent groups: dashes indicate significant difference.

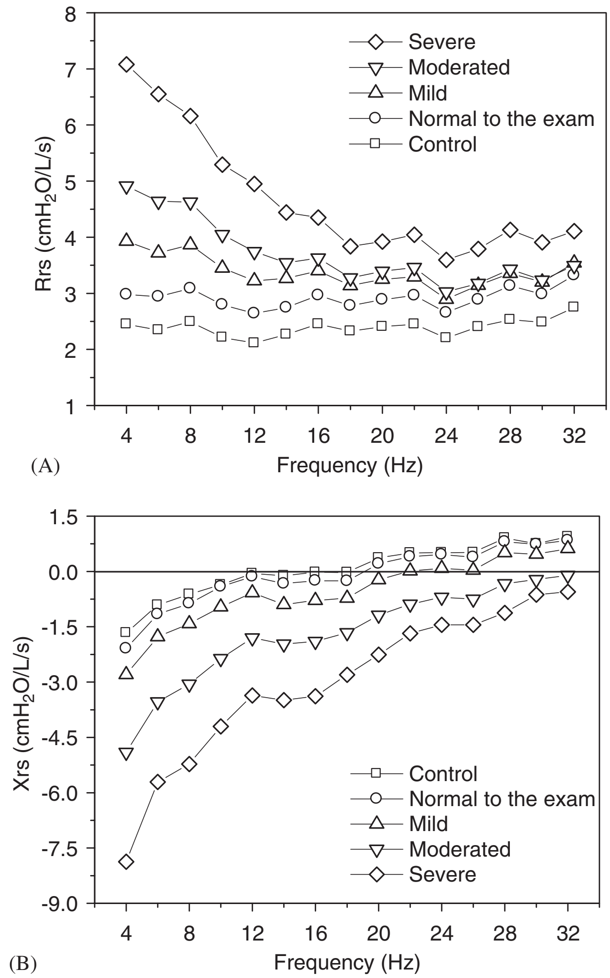

Figure 1 Comparisons of the mean values of respiratory system resistance (A) and reactance (B) as a function of frequency in control and asthmatic subjects.

age, weight and height. All of the spirometric parameters showed significant reductions.

Figure 1 shows the mean Rrs and Xrs curves for the different levels of airway obstruction. Generally, we observed two types of curves. The first one was a flat Rrs curve observed for individuals present in the control and normal to the espirometric exam groups. The second type was found for the midly, moderately and severely obstructed asthmatic subjects, showing elevated values of Rrs and increasing levels of frequency-dependency of Rrs with airway obstruction (Fig. 1A). Interestingly, clear increases in Rrs can already be seen comparing the normal to the espirometric exam and the control groups.

Figure 1(B) shows that mean Xrs curves in asthmatics were significantly changed with respect to the control group. The decrease of Xrs was proportional to the airway obstruction, being more marked at lower frequencies, which resulted in an increase of the resonant frequency. In contrast to Rrs results, no clear modifications in Xrs can be seen comparing the normal to the espirometric exam and the control groups.

The influence of airway obstruction in the resistive properties of the respiratory system of the studied patients is described in Fig. 2. In the present study, all the mean values of the resistive parameters showed statistically significant modifications ($P<0.0001$). There were not statistically significant differences between the control and NE groups, in contrast with the significant increases observed between control and mild groups. Although visually clear, the modifications between the mild and moderate subjects were not statistically significant. Mean values of R0, Rm and S increased significantly when groups of asthmatic patients with moderate and severe airway obstruction were compared.

Figure 3 describes the influence of airway obstruction in the reactive properties of the respiratory system of the studied patients. All parameters showed significant alterations among the studied groups ($P<0.001$). Considering variations between adjacent classes, significant modifications were observed in Xm in almost all comparisons. On the other hand, only few comparisons carried out with Crs, dyn and fr presented significant modifications. It is interesting to note that, although the differences between the control and NE groups were nonsignificant in all of the cited parameters, similar comparison between control and mild groups were always significant.

ROC curves are shown in Fig. 4, and the respective values of sensitivity, specificity, area under the curve and the cut-off points are given in Table 3.

Discussion

Previous works[7,8] have compared groups of controls and adult asthmatics observing clear modifications in FOT parameters. This raises the question: Is the FOT able to detect the changes in respiratory mechanics due to increasing degrees of airways obstruction in asthmatics? In fact, only one study has addressed this question.[13] However, the cited study used an Impulse Oscillation System, which has differences from the classical FOT, including data processing and the parameters used to interpret raw data.[4,28] Thus, to contribute to elucidate this question, this study investigated the possibility of detection the changes in respiratory mechanics in progressive airway obstruction in adult asthmatic patients by the classical FOT. It has been shown

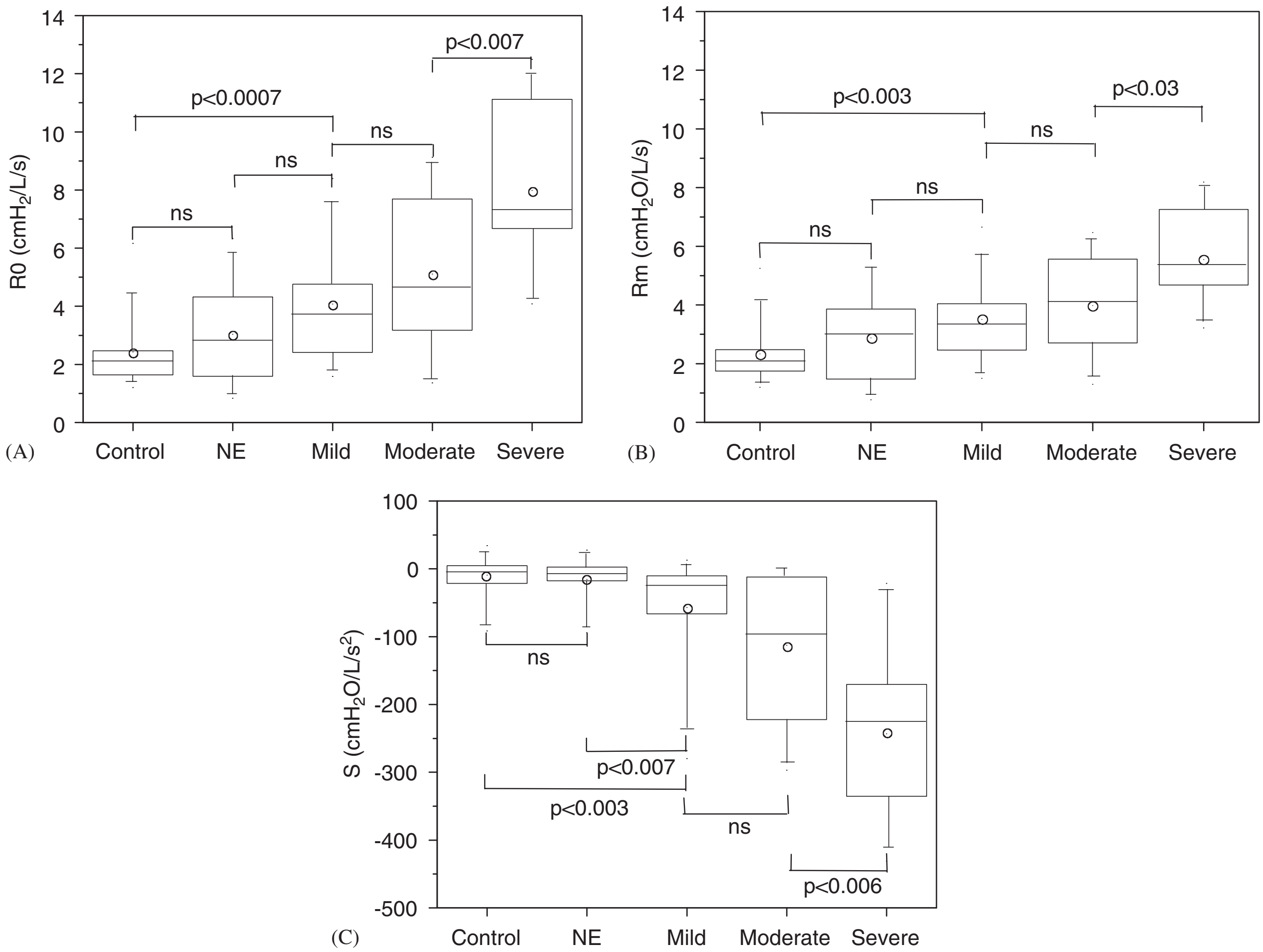

Figure 2 Resistive parameters, R0 (A), Rm (B) and S (C) in control and asthmatic patients according to bronchial obstruction severity. The top and the bottom of the box plot represent the 25th- to 75th-percentile values, while the bar across the box represents the 50th-percentile value. The whiskers outside the box represents the 10th- to 90th-percentile values, while the circle inside the box represents the median value.

that, as airway obstruction increased, Rrs increased and Xrs became more negative. Resistive and reactive FOT parameters presented important modifications, mainly in low airway obstruction and in advanced phases. These results were in close agreement with physiological fundamentals, supporting and adding new information to the results reported previously by other researchers and suggesting that FOT may be useful in the evaluation of respiratory mechanics of asthmatic patients.

Subjects and airway obstruction classification

We have performed a study in healthy subjects and asthmatics with a similar design to our previous report, which investigated the ability of FOT to detect the effects of COPD in respiratory mechanics.[16] The five studied groups were of comparable age, weight and height, showing only non-significant statistical differences (Table 1). In the studied groups, the modifications in spirometric parameters were non-significant comparing control and NE groups. The reductions in FEF_{25-75}/FVC and FEV_1/FVC were highly significant in the comparison among control and mild groups. In contrast, FEV_1/FVC presented higher reductions considering moderate and severe groups. The reductions in FEV_1(%pred) were significant in the comparison among control, mild, moderate and severe groups.

Respiratory impedance curves

In agreement with previous studies,[4,21,23] resistance values obtained in healthy volunteers were maintained constant throughout the frequency range investigated. Pasker et al.[29] verified that there was a progressive increase of Rrs and that the dependence of Rrs with the frequency became more negative with the increase of airway obstruc-

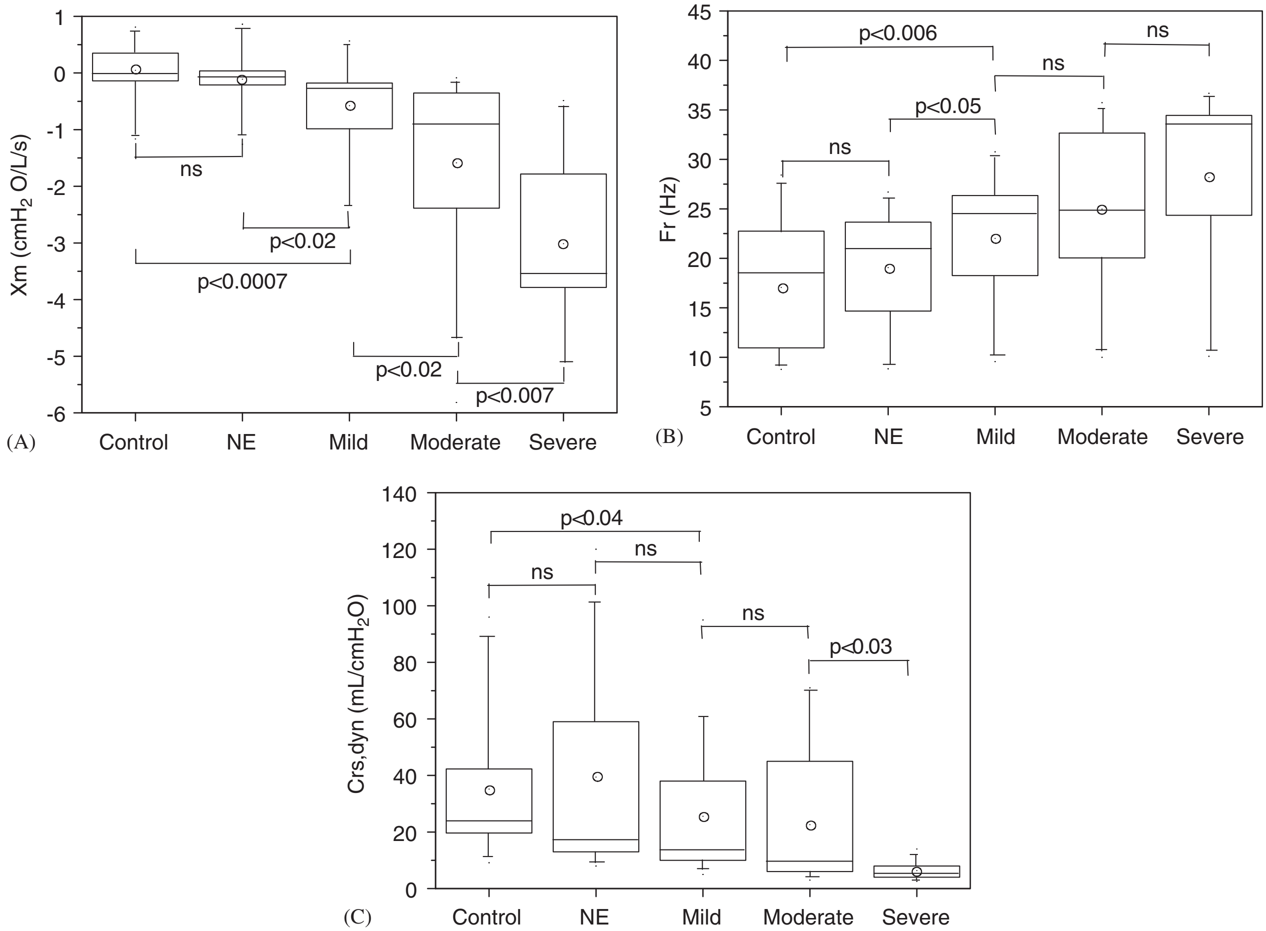

Figure 3 Box plot description of reactive parameters, Xm (A), fr (B), and Crs,dyn (C) in control and asthmatic patients according to airway obstruction.

tion in obstructive diseases. In the present study, this pattern was confirmed with the increase in the airway obstruction observed for asthmatic patients. In agreement with the cited study and other studies conducted in asthmatic patients,[29–31] Fig. 1(A) shows higher values of Rrs in asthmatics than in the control group. Even in the group composed by patients with normal spirometry, a clear increase in Rrs can be observed. Moreover, further increases in the spirometric classification are closely associated with increments in Rrs. Proportional increases in its frequency dependence can also be seen, mainly in the 4–16 Hz frequency range, which is in close agreement with the observations of Wouters.[32] According to Clément et al.[30] and Van Noord et al.,[8] these alterations constitute a characteristic pattern in the diseases with obstructive nature. The results described in Fig. 1(A) are in agreement with the recent work of Kaminsky and collaborators,[33] which studied the mechanical properties of the lung periphery in healthy and mildly asthmatic subjects, suggesting that the resistance of the lung periphery of the last ones is not well distinguished from that observed for healthy subjects.

Lutchen and Gillis[34] simulated central and peripheric bronchial constrictions in a dog lung model with the aim of analyze the alterations in pulmonary resistance (Rl). The authors studied two distinct situations: homogeneous airway constriction, where a uniform increase in Rl over the frequency range studied (1–8 Hz) was obtained, and (2) heterogeneous bronchial peripheral constriction, that resulted in extreme increases in the frequency dependency of Rl. The results described in Fig. 1(A) are in close agreement with the cited work, since in the control and NE groups a uniform increase in Rrs reflects a system with small non-homogeneities. On the other hand, in more advanced stages of airway obstruction, a progressive increase in the frequency-dependence of Rrs is clearly observed, reflecting the increased presence of more heterogeneous bronchial constriction.

Figure 1B describes the Xrs curves. In the control group, Xrs presented values slightly negative in low frequencies with an fr around 17 Hz, results that are coherent with previous works.[16] Asthmatic patients presented more negative values of Xrs in low frequencies. This behaviour became more evident with the reduction of the flows and volumes evaluated by the spirometry. Kim et al.[13] suggested that the progression of the airway obstruction in asthmatic patients increases the non-homogeneity, which is reflected by a fall in Xrs. Earlier studies conducted in patients with asthma and COPD also presented greater negative reactance in response to increased airflow obstruction.[30] Nagels et al.[35] related such findings to a non-homogeneous behaviour of the respiratory system. This can also be explained by the frequency dependent decreasing of lung compliance in airflow obstruction.[36]

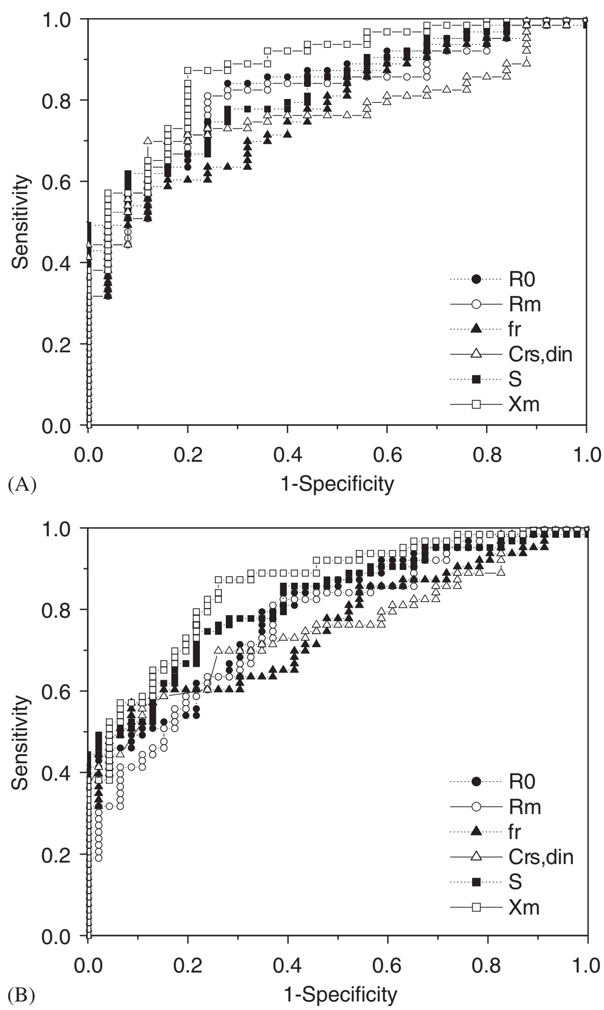

Figure 4 Receiver operating characteristic (ROC) curves for FOT parameters obtained excluding the asthmatics with normal response by spirometry (A), and including these asthmatics in the control group (B). Derived parameters are described in Table 3.

Resistive properties of the respiratory system

Mean values of resistive parameters in normal subjects are similar to that described previously in the literature.[23,29,37–39] In asthmatic patients, bronchoconstriction and inflammatory processes are known to reduce the internal airways diameter, thus increasing airways resistance.[40] In the present study, these effects are clearly illustrated by the significant increase observed in R0 (Fig. 1A) and Rm (Fig. 1B).

The increase of R0 in asthmatics when compared to healthy individuals was also observed in adults by Lorino et al.[24] and in children by Mazurek et al.[41] Although there is a visually clear increase of the R0 values in the NE group, reflecting the early stages of worsening of the airway obstruction, it was not significant. Airway changes in asthma usually begin at the peripheral airways. The resistance of the peripheral airways has also been shown to increase in asymptomatic asthmatic patients with normal spirometric values.[42] However, the contribution of this resistance to the total lung resistance is less than 10% because the volume and surface area of the lungs increase with airway generations.[43] This may, at least in part, explain the small increase of R0 in the NE group. Significant differences were observed comparing the control and mild groups. It seems to be reasonable that they could be explained by a more pronounced increase of the peripheral airway

Table 3 Values of area under the curve, sensitivity and specificity for the optimal cut-off points for the FOT indices.

	AUC	Sensitivity (%)	Specificity (%)	Cut-off point
R0 ($cmH_2O/L/s$)	0.84/0.80	81/71	76/70	2.59/3.23
Rm ($cmH_2O/L/s$)	0.81/0.77	81/71	76/67	2.48/3.16
S ($cmH_2O/L/s^2$)	0.82/0.82	78/78	72/72	−17.43/−17.42
Xm ($cmH_2O/L/s$)	0.88/0.86	81/79	80/78	−0.21/−0.21
Fr (Hz)	0.77/0.75	70/65	68/63	19.91/21.33
Crs,dyn (mL/cmH_2O)	0.77/0.75	73/70	72/70	19.74/15.62

Values not including the NE group / values including the NE group. AUC: area under curve.

resistance. However, conflicting results have been reported concerning peripheral airway resistance in mildly asthmatic subjects. Recently, Kaminsky and collaborators[33] suggested that this resistance can be not well distinguished from that of healthy subjects. On the other hand, Wagner et al.,[44] studying mild asthmatics with normal spirometry, reported that peripheral airway resistance was increased up to sevenfold, when compared with control individuals. Additional factors may contribute to the increase of R0. In the airway wall of asthmatic subjects, extensive thickening of the basement membrane, due to subepthelial fibrosis, is commonly observed even in an early stage.[45] Moreover, airway remodelling may result in increased wall area, which could introduce reductions in luminal area, contributing to the increase of R0 in the mild group. R0 continued to increase among the mild, moderate and severe stages. This may cause flow to be shunted into upper airways wall expansion.[3–6] The support of the mouth floor and the cheeks is not sufficient to eliminate the shunt effect. Therefore, a component of the measured input flow is lost in the motion of the compliant upper airway walls. This effect is minimal at low frequency and becomes increasingly important as oscillation frequency rises, resulting in the underestimation of high R0 values. Despite of this effect, a significant increase in R0 was observed comparing the mild and severe groups. It suggests that R0 could be useful to detect the initial airway obstruction changes in asthma and to qualify airway obstruction severity, mainly in the more advanced stages of this disease.

As illustrated in Fig. 2B, Rm tends to increase with the progression of the airway obstruction. These results are in line with studies conducted in obstructive diseases[30,38,46] and provide additional support to the interpretation of this parameter as being associated with the central airways.[4] There are evidences to suggest that airway inflammation occurs in all parts of the airway in asthmatics.[43] The entire airway wall is thickened, and the percentage of cross-sectional area of the airway occupied by airway wall tissue is increased by 1.5 to 2-fold.[45] Both mechanisms could introduce reductions in luminal area in the central airway, which may explain the results described in Fig. 2(B). The comparisons between groups were similar to R0, with significant differences between control and mild groups, and between the moderate and severe groups. This suggests the usefulness of Rm as an indirect index of airway obstruction severity, which may be able to detect early changes and advanced airway obstruction in asthma.

In contrast to previous works, which reported S values near zero in normal subjects,[22,39] our control group exhibited slightly negative S values (Fig. 2C). This discrepancy may be associated with the older age of our control group.[16,47,48] In the early stages of obstructive lung disease, it is likely that an increased non-uniform distribution of mechanical time constants occurs along different ventilation pathways. This could introduce enlarged inhomogeneities, being consistent with the results described in Fig. 2C for the normal to the exam and mild groups. As pointed out earlier, the shunt effect associated with the increase in lung resistance is minimal at low frequency and becomes increasingly important as oscillation frequency rises, leading to an artefactual frequency-dependency of Rrs.[6] This way, besides respiratory system non-homogeneity, airway wall shunt probably plays an important role in the S results described in Fig. 2C, mainly in the more advanced stages of airway obstruction. The difference between the control group and the NE group was not significant, probably because the non-homogeneity of the NE subjects has not been severe enough to reach statistical significance. A significant modification was observed comparing the groups NE and mild, suggesting that S could be useful to detect early modification in respiratory mechanics of asthmatic patients. This result is in line with the studies conducted by Pairon et al.[37] and Pham et al.[38] In more advanced stages of airway obstruction (moderate and severe), S reflected the decrease in the homogeneity of the respiratory system in these patients. Kaczka et al.[49] investigated the airway and lung tissue mechanics in asthmatics with mild and moderate-to-severe airway obstruction. In line with the results described in Fig. 2C, these authors reported a higher frequency-dependent profile of lung resistance in patients with moderate-to-severe airway obstruction, which was related in the cited work to airway constriction in the lung periphery. More negative S values in adult asthmatic subjects were also observed by Zerah et al.[11] and Noord et al.[8] However, the modifications in S were qualitatively similar to that observed in emphysematous,[8,50] kyphoscoliosis[51] and COPD[16,52] patients. Therefore, this parameter does not offer the distinction between the restrictive and obstructive changes, although it seems to be a promising non-specific index of mechanical non-homogeneities.

Reactive properties of the respiratory system

In the present work, the control group showed reactive properties similar to that obtained in previous studies.[16,29,31,39,52–54] Mean reactance is usually related to respiratory system non-homogeneities.[27] Thus, the highly significant modification in Xrs (Fig. 3A) may be explained by the increase in mechanical non-homogeneities with the worsening of airway obstruction. It can be conjectured that inflammation and airway wall remodelling may be involved in this process. More extensive remodelling increases the likelihood of random airway closure, a constriction pattern for which the mechanical non-homogeneities are increased. These results were consistent with that obtained in asthmatics by Noord et al.[8] and in obstructive patients[30] and may result from a combination of reduced respiratory system compliance, higher peripheral resistance effects, and upper airway shunt. As observed in resistive parameters, the upper airway shunt may also play an important role in the Xm results. In conditions of high airway obstruction its effect introduces a shift in Xrs to higher frequencies, also increasing fr.[6] Despite of this, Xm was the only parameter able to achieve significant modifications comparing the mild and moderate stages. This parameter also showed significant modifications in early as well as in more advanced stages of airway obstruction, and seems to be promising as an indirect index of airway obstruction.

In this work, the fr in the control group presented higher values than that reported by other researchers (Fig. 3B).[7,23,31,37,39] As earlier discussed for S, this result can be easily explained considering the older age of our control group.[47,48] In line with previously reported results, the resonance frequency in the asthmatic subjects were higher than that obtained in the control group.[8,29] The growing behaviour of fr with airway obstruction is in agreement with the results obtained by Kim et al.[13] Asthma has an important inflammatory component, which is known to involve the lung periphery. Moreover, airway smooth muscle shortening is predicted to lead to enhance peripheral constriction in the setting of airway wall inflammation and remodelling.[55] The increase in fr probably describes the non-homogeneities that resulted from regional hyperinflation and air trapping introduced by the cited changes. Cauberghs and Woestijne[7] considered fr useful to discriminate between healthy subjects and obstructive patients. The results presented in Fig. 3B are in line with those presented by the cited authors, since significant differences were observed comparing control with mild, moderate and severe groups. The difference between the control and the mild groups were significant. However, it was not possible to discriminate adjacent groups in more advanced airway obstruction stages using this parameter. Thus, it is suggested that fr could be useful to detect asthma in its initial airway obstruction changes, even thought it is not adequate to qualify obstruction severity.

A significant decrease in Crs,dyn was observed with airway obstruction (Fig. 3C). Since the dynamic compliance includes the lungs and bronchial wall compliances, the compliance of the chest wall/abdomen compartment and thoracic gas compression,[4,56] several factors may be involved in this result. Long-standing airway inflammation in asthma can lead to airway remodelling. Hence asthmatic patients have increased airway wall area, the degree of which depends on disease severity.[57] Thus a progressive reduction of airway wall compliance coherent with the results described in Fig. 3(C) may be expected. In support of this theory, it was suggested that chronic airway inflammation and/or remodelling in asthmatic individuals might lead to a decreased compliance of the central airways.[45] The deformation of the thoracic wall associated with lung hyperinflation, usually found in such patients, may be another possible explanation, because it introduces an important restrictive factor in the interaction between the lung and thoracic wall. Tulic et al.[43] pointed out that an uncoupling of the parenchyma and airways due to the mechanical interdependence between these two compartments might be caused by the small airway inflammation. Moreover, structural effects in central airways, inflammatory and structural changes also occur in lung parenchyma,[43] which, theoretically, may also be included in the variations of Crs,dyn. The frequency dependence of dynamic compliance due to non-uniform ventilation[40] also needs to be considered, since the airway wall remodelling and inflammation that occurs in asthma predisposes the lung to a more heterogeneous pattern of peripheral airway constriction. In this way, the reduction of Crs,dyn in the studied asthmatic subjects likely reflects the progressive functional consequences of airway inflammation and remodelling, as well as the reduction in the compliance of the respiratory system. It is also important to point out that Crs,dyn also includes the compliance of the upper airway, associated with the soft tissues of the mouth, cheeks and pharynx.[3–5,6,56] Similar to Xm, Crs,dyn showed significant statistically differences between the control and mild groups, and between the moderate and severe groups. However, in contrast to Xm, it has not been observed significant differences between the mild and moderate groups and the mild and NE groups, which suggests that Crs,dyn could be useful to detect asthma, although it is not adequate to qualify airway obstruction severity.

Increases in asthma airflow obstruction and FOT parameters

There is not a consensus in the literature concerning what are the better parameters to evaluate respiratory mechanics by FOT. In this study with asthmatic subjects, all of the studied FOT parameters were able to discriminate patients with mild obstruction from normal subjects. Considering the modifications between adjacent classes, the most sensitive measurements for detecting the effects of the initial phases of airway obstruction were first, Xm, with significant changes between the NE and mild groups, followed by R0, and S. Mean reactance was the only parameter sufficiently selective to separate subjects with mild and moderate obstruction. In more advanced stages, Xm, R0, and S were the most sensitive to describe the effects in moderate and severe patients.

Comparing the behaviour of FEV_1(% pred) and FEV_1/FVC (Table 2) with FOT parameters, it can be observed that in the early stages, including control, NE and mild groups, the behaviour of these spirometric parameters were similar to that of R0, Rm, S (Fig. 2), Xm and fr (Fig. 3). Comparing mild and moderate groups, only Xm was able to separate the groups. Therefore, resistive FOT parameters were not as selective as the espirometric parameters. On the other hand, in comparisons between moderate and severe groups, almost all of the studied FOT parameters were as selective as the espirometric indexes. This suggests that the cited FOT parameters may be used as a complement to spirometry in order to help the detection of early changes (e.g. mild vs. control), and that they may also be helpful to qualify severity in asthma.

FOT as a diagnostic test: sensitivity and specificity of FOT indices

The ROC curves plots the probability of true-negative (specificity) versus the probability of false-positive (1-sensitivity) for various decision criteria. This way, the larger the area under the curve (AUC), more valid the diagnostic test in comparison with the gold standard (spirometry in this case).[46] An area under the ROC curve >0.80 is considered adequate.[58] R0, Rm, S and Xm achieved an acceptable value when the NE group was excluded. In this conditions, Xm measurements were the most adequate to correctly identify asthmatic patients, with a sensitivity of 81% and a specificity of 80%. As expected, the inclusion of patients with normal spirometry causes a reduction in the diagnostic value of the FOT parameters (Fig. 4B, Table 3). Even in this adverse situation, S and Xm were able to obtain adequate values of AUC, while R0 reaches the limit value (0.80). Among all the studied parameters, Xm was the best of them, showing a sensitivity of 79%, a specificity of 78%, and AUC of 0.86.

Limitations of this study

Because of interference with the subject's breathing signal, random and systematic errors may be introduced around the low frequency range.[3–6] In the present work, the reliability of the results was guaranteed using a minimal coherence function of 0.9. The upper airway shunt may introduce underestimations in the resistance value, but providing firm support of the cheeks and mouth floor, as performed by the present subjects, effectively reduces the errors due to movement in upper airway wall[52] although they could not be totally removed. Even tought FOT is very easy to carry out, caution has always to be taken to avoid the flexion of the neck, which may result in a narrowing of the hypopharynx and to make measurements at the level of FRC.

Conclusions

In the studied population of adult asthmatic subjects, this disease introduced modifications in FOT resistive and reactive parameters that were proportional to the intensity of airway obstruction. An important increase in respiratory system resistance and a reduction of respiratory system homogeneity were observed in all phases of airway obstruction, which are in close agreement with the asthma pathophysiology. Accordingly, the parameters with the highest sensitivity and specificity for identifying asthmatic patients were R0, Xm and S.

Spirometry demands high co-operation from the patient, and can lead to temporary alteration in bronchomotor tone due to the deep inspiration required, which can have implications for respiratory mechanics measurements. FOT requires only tidal breathing and is easy to perform. These practical considerations, together with the results of the present study, indicates that FOT may give a significant clinical contribution in the evaluation of asthmatic subjects, representing a promising solution to the problem of effort dependence.

Acknowledgements

The authors which to thank Mesquita Jr., J.A., Santos, J.G., and Faria, A.C. for their assistance. This study was supported by FAPERJ and CNPq.

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